

Is Routine Metformin Discontinuation Necessary Before Elective Coronary Angiography? A Randomized Clinical Trial

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Research Article

Keywords: Metformin, Coronary angiography, Contrast-induced acute kidney injury, Lactic acidosis, Randomized clinical trial

Posted Date: March 26th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-8979165/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background:

The optimal peri-procedural management of metformin in patients with type 2 diabetes undergoing elective coronary angiography remains debated. Concerns regarding contrast-induced acute kidney injury (CI-AKI) and the potential risk of metformin-associated lactic acidosis (MALA) have led to varying clinical practices, despite evolving evidence. Furthermore, limited data exist regarding the influence of metformin dosage and baseline renal function on post-procedural renal and metabolic outcomes. This randomized clinical trial aimed to evaluate the safety of continuing metformin therapy during elective coronary angiography and to assess the impact of metformin dose and pre-procedural renal status on subsequent laboratory changes.

Methods:

In this prospective, open-label randomized study, 204 adults with type 2 diabetes receiving metformin and scheduled for elective coronary angiography at Heshmat Hospital, Rasht, Iran, were randomly assigned to either continue metformin therapy (n = 102) or discontinue metformin 24 hours before the procedure with resumption 72 hours afterward (n = 102). Serum creatinine, estimated glomerular filtration rate (eGFR), plasma lactate concentration, and arterial pH were assessed at baseline and 72 hours following angiography. Between-group comparisons were conducted using appropriate statistical tests. Multivariable regression analysis was performed to adjust for baseline laboratory values, metformin dose, contrast volume, age, body mass index, and sex.

Results:

No statistically significant differences were observed between the continuation and discontinuation groups in post-procedural serum creatinine, eGFR, lactate levels, or arterial pH (all $P > 0.05$). Baseline renal and metabolic parameters were the strongest predictors of post-angiography values. Higher daily metformin doses (1500–2000 mg) were associated with modest increases in serum creatinine and lactate; however, these changes were not clinically significant and were not accompanied by meaningful alterations in arterial pH.

Conclusion:

Among patients with type 2 diabetes and preserved renal function undergoing elective coronary angiography, continuation of metformin therapy did not increase the risk of CI-AKI or clinically relevant metabolic disturbances. These findings support an individualized approach to peri-procedural metformin management rather than routine discontinuation.

Introduction

Metformin is the cornerstone pharmacologic treatment for type 2 diabetes mellitus and remains the preferred initial therapy due to its well-documented effects on glycemic control, metabolic parameters, and cardiovascular risk reduction (1). Because the medication is cleared almost entirely through renal excretion, clinical concern has traditionally focused on the possibility of drug accumulation when kidney function acutely declines (2). This concern stems from the feared development of metformin-associated lactic acidosis (MALA), an uncommon yet serious adverse event that has historically shaped conservative prescribing practices (3).

In cardiology, coronary angiography with iodinated contrast agents is routinely performed for both diagnostic and therapeutic purposes (4). While contrast-induced acute kidney injury (CI-AKI) has long been regarded as a significant procedural risk, more recent investigations suggest that its incidence is lower than previously assumed, particularly in clinically stable individuals with preserved baseline renal function (5). Importantly, reported episodes of lactic acidosis among metformin-treated patients have most often occurred in the presence of substantial comorbid conditions, such as severe infection, advanced chronic kidney disease, or acute heart failure, rather than as a direct consequence of contrast administration alone(6).

Nevertheless, many institutions continue to recommend temporary discontinuation of metformin before and after contrast exposure, despite limited supporting evidence (7). This precautionary strategy may result in short-term worsening of glycemic control without demonstrable clinical benefit (8). As contemporary international recommendations increasingly re-evaluate the necessity of routine metformin interruption, there is a clear need for rigorous prospective data to guide practice (9).

Accordingly, this randomized clinical trial was undertaken to evaluate the safety of maintaining metformin therapy compared with temporarily withholding it in patients with type 2 diabetes undergoing elective coronary angiography. The primary objective was to assess renal and metabolic outcomes and determine whether continuation of metformin is safe in patients with adequate baseline kidney function.

Methods

Study Design and Setting

This randomized, open-label clinical trial was conducted at Heshmat Hospital, Rasht, Iran, from 2023 to 2024. The study included participants who met predefined inclusion and exclusion criteria and were randomly assigned to study groups. Data collection, interventions, and follow-up procedures were carried out at the hospital under standardized conditions. The trial was registered with the Iranian Registry of Clinical Trials (IRCT: IRCT20240821062831N1).

Study Population

Eligible participants included patients aged 30–70 years with type 2 diabetes mellitus receiving metformin therapy who were scheduled for elective coronary angiography. Exclusion criteria were: emergency angiography, contraindications to metformin (e.g., decompensated heart failure, severe hepatic disease, or severe hypoxemia), acute or chronic metabolic acidosis, and baseline GFR < 45 mL/min/1.73 m². Patients who did not complete the study protocol or withdrew consent were excluded from the analysis. This trial specifically represents a contemporary low-risk elective angiography population, characterized by preserved baseline renal function, iso-osmolar contrast use, and standardized hydration protocols.

Sample Size and Randomization

Sample size was calculated based on the results of the study by *Impact of continuation of metformin prior to elective coronary angiography on acute contrast nephropathy in patients with normal or mildly impaired renal functions* (10). Assuming a mean post-angiography eGFR of 82 ± 19 mL/min/1.73 m² in the continuation group and 74 ± 12 mL/min/1.73 m² in the withholding group, with 90% power and $\alpha = 0.05$, a minimum of 85 patients per group was required. Considering a 20% dropout rate, 102 patients per group were enrolled, yielding a total of 204 participants. Patients were randomly assigned to either continue metformin until the day of angiography or withhold metformin 24 hours prior and resume 72 hours post-procedure.

Randomization

After screening and confirming eligibility, 204 patients meeting all inclusion criteria were enrolled in the study. Participants were randomly assigned in a 1:1 ratio to one of two groups:

1. **Continue Metformin Group (n = 102):** Patients who continued their usual metformin therapy up to the day of coronary angiography.
2. **Stop Metformin Group (n = 102):** Patients who discontinued metformin 24 hours prior to the procedure and resumed therapy 72 hours after angiography.

Randomization was performed using a computer-generated random sequence, with allocation concealed in sequentially numbered, sealed opaque envelopes to ensure allocation concealment and minimize selection bias.

Blinding

This study was conducted as an open-label trial. Both participants and treating clinicians were aware of the assigned intervention. However, laboratory personnel who analyzed serum creatinine, lactate, and pH levels were blinded to group allocation to minimize detection bias.

Endpoints

The primary endpoint was the change in serum creatinine from baseline to 72 hours after elective coronary angiography, with additional assessment of renal recovery or persistence of change at 1 month. Secondary endpoints included changes in serum creatinine at 1 month, estimated glomerular filtration rate (eGFR), plasma lactate, and arterial pH within 72 hours after the procedure. Exploratory analyses evaluated dose- and baseline renal function–related patterns in renal and metabolic parameters.

Data Collection and Outcome Assessment

Demographic and clinical data, including age, sex, height, weight, metformin dose, contrast volume, ejection fraction (EF), and fasting blood glucose (FBS), as well as concomitant medications (other antidiabetic agents, ACE inhibitors, ARBs, MRAs, and diuretics) were recorded by study staff using a structured case report form to ensure blinding of data collection.

Contrast agent

All patients received iodixanol, an iso-osmolar contrast medium chosen for its minimal nephrotoxicity.

Laboratory measurements

Serum creatinine (Cr) levels were measured using a photometric method, based on the absorbance of light relative to known concentrations. Arterial blood gases (before and after angiography) and lactate levels (after angiography) were assessed using standard blood gas analyzers. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault formula (11).

- **For Men:** $\text{CrCl (mL/min)} = [(140 - \text{age}) \times \text{weight (kg)}] / (72 \times \text{serum creatinine (mg/dL)})$.
- **For Women:** Multiply the result by 0.85.

Serum creatinine was re-evaluated one month after angiography to assess return to baseline values.

Statistical Analysis

All patient data were analyzed using SPSS version 22. Continuous variables were presented as mean $\pm$ standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Normality of continuous variables was assessed using the Kolmogorov-Smirnov test.

Comparisons between categorical variables were performed using Chi-square or Fisher's exact tests, as appropriate. For continuous variables, independent t-tests were applied for normally distributed data, and Mann-Whitney U tests were used for non-normally distributed data. Within-group comparisons of pre-

and post-procedure values were conducted using paired t-tests or Wilcoxon signed-rank tests, depending on data distribution.

To evaluate the effect of metformin continuation versus discontinuation on renal function, lactate levels, and acid-base status while controlling for potential confounders, multivariable analysis of covariance (ANCOVA) models were fitted. These models adjusted for baseline values of the outcome variable, metformin dose, contrast volume, age, BMI, and gender. Effect sizes were reported as partial eta squared, and statistical significance was set at $p < 0.05$. Dose- and contrast volume-stratified analyses were additionally performed to explore potential dose-dependent or procedure-related effects.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki (12). Written informed consent was obtained from all participants prior to enrollment. The study protocol was reviewed and approved by the institutional ethics committee (IR.GUMS.REC.1403.221). The trial was registered with the Iranian Registry of Clinical Trials (IRCT: IRCT20240821062831N1). All potential risks, benefits, and study procedures were thoroughly explained to participants, and voluntary participation was ensured.

Results

Patient Characteristics

A total of 204 patients undergoing coronary angiography were included in the study, evenly divided into two groups: metformin discontinuation ($n = 102$) and continuation ($n = 102$). Baseline demographic characteristics were similar between groups (Table 1). The mean age was 57.78 ± 8.47 years in the discontinuation group and 56.19 ± 6.00 years in the continuation group ($P = 0.195$). BMI was comparable (26.45 ± 2.80 vs 26.70 ± 2.60 kg/m²; $P = 0.312$). The gender distribution was balanced, with males comprising 57.8% of the discontinuation group and 56.9% of the continuation group ($P = 0.742$).

Table 1
Comprehensive Comparison of Baseline Characteristics, Clinical Variables, and Outcomes Between Study Groups

Variable	Category / Time Point	Stop Metformin (n = 102)	Continue Metformin (n = 102)	P-value
Demographic Characteristics				
Gender, n (%)	Male	59 (57.84)	58 (56.86)	0.742†
	Female	43 (42.16)	44 (43.14)	
Age (years), Mean (SD)	—	57.78 (8.47)	56.19 (6.00)	0.195‡
BMI (kg/m²), Mean (SD)	—	26.45 (2.80)	26.70 (2.60)	0.312‡
Underlying Diseases, n (%)				
Hypertension (HTN)	No	44 (43.14)	52 (50.98)	0.262†
	Yes	58 (56.86)	50 (49.02)	
Heart Failure (HF)	No	75 (73.53)	82 (80.39)	0.244†
	Yes	27 (26.47)	20 (19.61)	
Chronic Kidney Disease (CKD)	No	102 (100.0)	98 (96.08)	0.061‡
	Yes	0 (0.00)	4 (3.92)	
Dyslipidemia (DLP)	No	21 (20.59)	17 (16.67)	0.472†
	Yes	81 (79.41)	85 (83.33)	
Concomitant Medications, n (%)				
ACE Inhibitors	Not use	61 (59.80)	62 (60.78)	0.886†
<i>Comparison of baseline characteristics, comorbidities, medication use, renal, metabolic, and procedural parameters between patients who discontinued versus continued metformin therapy before coronary angiography</i>				
Statistical Notes				
• Data are presented as Mean (SD) or n (%)				
• † Pearson Chi-Square test				
• ‡ Mann-Whitney U test				
• § Friedman or Wilcoxon Signed Ranks test (within-group analysis)				

Variable	Category / Time Point	Stop Metformin (n = 102)	Continue Metformin (n = 102)	P-value
	Use	41 (40.20)	40 (39.22)	
ARB	Not use	94 (92.16)	89 (87.25)	0.249†
	Use	8 (7.84)	13 (12.75)	
MRA	Not use	75 (73.53)	82 (80.39)	0.244†
	Use	27 (26.47)	20 (19.61)	
Diuretics	Not use	96 (94.12)	97 (95.10)	0.757†
	Use	6 (5.88)	5 (4.90)	
Insulin	Not use	91 (89.22)	93 (91.18)	0.219†
	Use	11 (10.78)	9 (8.82)	
Other antidiabetic drugs	Not use	72 (70.59)	77 (75.49)	0.134†
	Use	30 (29.41)	25 (24.51)	
Renal Function (Creatinine)				
Creatinine (mg/dL)	Before angiography	0.98 (0.06)	0.97 (0.06)	0.372‡
	After angiography	1.02 (0.05)	1.04 (0.06)	0.198‡
	One month after	0.99 (0.06)	1.00 (0.05)	0.453‡
Within-group P-value	—	0.071§	0.063§	
Cardiac & Procedural Variables				
<i>Comparison of baseline characteristics, comorbidities, medication use, renal, metabolic, and procedural parameters between patients who discontinued versus continued metformin therapy before coronary angiography</i>				
Statistical Notes				
• Data are presented as Mean (SD) or n (%)				
• † Pearson Chi-Square test				
• ‡ Mann-Whitney U test				
• § Friedman or Wilcoxon Signed Ranks test (within-group analysis)				

Variable	Category / Time Point	Stop Metformin (n = 102)	Continue Metformin (n = 102)	P-value
Ejection Fraction (%), Mean (SD)	—	49.22 (7.06)	49.36 (6.12)	0.504‡
Contrast volume (mL), Mean (SD)	—	98.10 (5.80)	98.45 (5.50)	0.650‡
Contrast volume, n (%)	80 mL	6 (5.88)	7 (6.86)	0.777†
	100 mL	96 (94.12)	95 (93.14)	
Metformin dose (mg/day), Mean (SD)	—	1020.58 (500.00)	1045.65 (475.00)	0.592‡
Metformin dose, n (%)	500	30 (29.41)	28 (27.45)	0.665†
	1000	28 (27.45)	29 (28.43)	
	1500	21 (20.59)	22 (21.57)	
	2000	23 (22.55)	23 (22.55)	
Metabolic & Acid–Base Parameters				
GFR (mL/min/1.73 m ²)	Before	80.00 (8.29)	85.00 (7.50)	0.196‡
	After	76.01 (7.90)	78.00 (7.40)	0.225‡
Within-group P-value	—	0.065§	0.058§	
Lactate (mmol/L)	Before	1.46 (0.12)	1.40 (0.10)	0.321‡
	After	1.49 (0.13)	1.50 (0.11)	0.341‡
Within-group P-value	—	0.062§	0.054§	
pH	Before	7.38 (0.01)	7.37 (0.02)	0.120‡
	After	7.38 (0.01)	7.37 (0.02)	0.115‡
<i>Comparison of baseline characteristics, comorbidities, medication use, renal, metabolic, and procedural parameters between patients who discontinued versus continued metformin therapy before coronary angiography</i>				
Statistical Notes				
• Data are presented as Mean (SD) or n (%)				
• † Pearson Chi-Square test				
• ‡ Mann-Whitney U test				
• § Friedman or Wilcoxon Signed Ranks test (within-group analysis)				

Variable	Category / Time Point	Stop Metformin (n = 102)	Continue Metformin (n = 102)	P-value
Within-group P-value	—	0.301§	0.288§	
<i>Comparison of baseline characteristics, comorbidities, medication use, renal, metabolic, and procedural parameters between patients who discontinued versus continued metformin therapy before coronary angiography</i>				
Statistical Notes				
• Data are presented as Mean (SD) or n (%)				
• † Pearson Chi-Square test				
• ‡ Mann-Whitney U test				
• § Friedman or Wilcoxon Signed Ranks test (within-group analysis)				

Comorbidities, including hypertension, heart failure, chronic kidney disease (CKD), and dyslipidemia, were similarly distributed. Notably, CKD was present in 4 patients (3.9%) in the continuation group and absent in the discontinuation group, but this difference was not statistically significant ($P = 0.061$). Concomitant medication use—including ACE inhibitors, ARBs, MRAs, diuretics, insulin, and other antidiabetic drugs—was comparable between groups.

Cardiac function and procedural characteristics were also similar. Mean ejection fraction was $49.22 \pm 7.06\%$ in the discontinuation group versus $49.36 \pm 6.12\%$ in the continuation group ($P = 0.504$). The mean contrast volume administered was 98.10 ± 5.80 mL vs 98.45 ± 5.50 mL ($P = 0.650$), with most patients receiving 100 mL (94.1% and 93.1%, respectively). Metformin dose distribution ranged from 500 to 2000 mg/day, with similar proportions in each dose category.

Renal Function by Metformin Dose

Renal outcomes stratified by metformin dose are summarized in Table 2.

Table 2

Metformin Dose–Stratified Comparison of Renal Function, Lactate Levels, and Acid–Base Status Between Patients Who Discontinued Versus Continued Metformin Therapy

Metformin Dose (mg/day)	Parameter	Time Point	Stop Metformin Mean (SD)	Continue Metformin Mean (SD)	P-value (Between Groups)
500	Creatinine (mg/dL)	Before angiography	0.96 (0.06)	0.96 (0.06)	0.980
		After angiography	0.99 (0.05)	1.00 (0.06)	0.250
		One month after	0.98 (0.06)	0.97 (0.06)	0.275
	GFR (mL/min/1.73 m²)	Before angiography	81.20 (6.50)	80.10 (7.50)	0.580
		After angiography	79.80 (6.40)	77.90 (7.40)	0.550
	Lactate (mmol/L)	Before angiography	1.42 (0.11)	1.45 (0.12)	0.380
		After angiography	1.43 (0.12)	1.47 (0.13)	0.370
	pH	Before angiography	7.37 (0.02)	7.37 (0.02)	0.301
		After angiography	7.37 (0.02)	7.37 (0.02)	0.287
1000	Creatinine (mg/dL)	Before angiography	0.95 (0.05)	0.96 (0.06)	0.298
		After angiography	0.99 (0.05)	1.01 (0.05)	0.240
		One month after	0.97 (0.06)	0.98 (0.05)	0.265
Dose-dependent effects of metformin (500–2000 mg/day) on renal function, lactate concentration, and acid–base status in patients who discontinued versus continued metformin therapy undergoing coronary angiography.					
Statistical Notes					
• Data are presented as Mean (SD)					
• Between-group comparisons: Mann–Whitney U test					
• Within-group comparisons: Friedman or Wilcoxon signed-rank tests					
• P < 0.05 considered statistically significant					

Metformin Dose (mg/day)	Parameter	Time Point	Stop Metformin Mean (SD)	Continue Metformin Mean (SD)	P-value (Between Groups)
1500	GFR	Before angiography	83.40 (6.00)	82.30 (7.20)	0.610
		After angiography	81.00 (6.10)	79.10 (7.00)	0.590
	Lactate	Before angiography	1.46 (0.13)	1.48 (0.11)	0.510
		After angiography	1.47 (0.13)	1.51 (0.12)	0.440
	pH	Before angiography	7.38 (0.02)	7.38 (0.02)	0.267
		After angiography	7.38 (0.02)	7.38 (0.02)	0.249
	Creatinine (mg/dL)	Before angiography	0.98 (0.06)	0.97 (0.05)	0.347
		After angiography	1.02 (0.06)	1.08 (0.06)	< 0.001
		One month after	0.99 (0.06)	1.00 (0.05)	< 0.001
	GFR	Before angiography	76.50 (3.20)	77.80 (6.50)	0.490
		After angiography	74.10 (2.80)	70.10 (5.80)	0.033
Lactate	Before angiography	1.45 (0.12)	1.46 (0.10)	0.620	
	After angiography	1.47 (0.13)	1.53 (0.11)	0.049	
Dose-dependent effects of metformin (500–2000 mg/day) on renal function, lactate concentration, and acid–base status in patients who discontinued versus continued metformin therapy undergoing coronary angiography.					
Statistical Notes					
• Data are presented as Mean (SD)					
• Between-group comparisons: Mann–Whitney U test					
• Within-group comparisons: Friedman or Wilcoxon signed-rank tests					
• $P < 0.05$ considered statistically significant					

Metformin Dose (mg/day)	Parameter	Time Point	Stop Metformin Mean (SD)	Continue Metformin Mean (SD)	P-value (Between Groups)
2000	pH	Before angiography	7.38 (0.02)	7.38 (0.02)	0.841
		After angiography	7.38 (0.02)	7.37 (0.02)	0.826
	Creatinine (mg/dL)	Before angiography	0.97 (0.06)	0.96 (0.06)	0.410
		After angiography	1.01 (0.06)	1.10 (0.05)	< 0.001
		One month after	0.98 (0.06)	1.01 (0.06)	< 0.001
	GFR	Before angiography	75.30 (4.00)	76.70 (7.00)	0.520
After angiography		72.60 (3.90)	69.00 (8.00)	0.028	
	Lactate	Before angiography	1.47 (0.10)	1.48 (0.11)	0.590
		After angiography	1.50 (0.11)	1.56 (0.12)	0.038
	pH	Before angiography	7.37 (0.01)	7.37 (0.01)	0.090
		After angiography	7.37 (0.01)	7.36 (0.01)	0.077
Dose-dependent effects of metformin (500–2000 mg/day) on renal function, lactate concentration, and acid–base status in patients who discontinued versus continued metformin therapy undergoing coronary angiography.					
Statistical Notes					
• Data are presented as Mean (SD)					
• Between-group comparisons: Mann–Whitney U test					
• Within-group comparisons: Friedman or Wilcoxon signed-rank tests					
• $P < 0.05$ considered statistically significant					

- Low to moderate doses (500–1000 mg/day): Serum creatinine measured before angiography, immediately after the procedure, and one month later did not differ significantly between the discontinuation and continuation groups ($P > 0.05$ for all comparisons). GFR, lactate, and pH

similarly showed no significant differences. Within-group analysis demonstrated no significant temporal changes.

- High doses (1500–2000 mg/day): Post-angiography creatinine was significantly higher in the continuation group than in the discontinuation group for both 1500 mg (1.08 ± 0.06 vs 1.02 ± 0.06 mg/dL; $P < 0.001$) and 2000 mg (1.10 ± 0.05 vs 1.01 ± 0.06 mg/dL; $P < 0.001$). At one month, creatinine remained elevated in the continuation group ($P < 0.001$). GFR was significantly lower after angiography in the continuation group at both 1500 mg (70.1 ± 5.8 vs 74.1 ± 2.8 mL/min/1.73 m²; $P = 0.033$) and 2000 mg (69.0 ± 8.0 vs 72.6 ± 3.9 mL/min/1.73 m²; $P = 0.028$). Lactate levels were elevated post-procedure in the continuation group for 1500 mg (1.53 ± 0.11 vs 1.47 ± 0.13 mmol/L; $P = 0.049$) and 2000 mg (1.56 ± 0.12 vs 1.50 ± 0.11 mmol/L; $P = 0.038$). No significant differences in pH were observed across doses.

These findings indicate a dose-dependent effect of metformin on post-angiography creatinine, GFR, and lactate, with higher doses associated with modest but statistically significant alterations in renal and metabolic parameters.

Renal and Metabolic Outcomes by Contrast Volume

Analysis by contrast agent volume (80 vs 100 mL; Table 3) revealed no statistically significant differences in creatinine, GFR, lactate, or pH between the discontinuation and continuation groups. Within-group comparisons also demonstrated no significant temporal changes, indicating that contrast volume did not significantly influence renal or metabolic outcomes in either group.

Table 3

Contrast Volume–Stratified Comparison of Renal, Metabolic, and Acid–Base Parameters Between Patients Who Discontinued Versus Continued Metformin Therapy

Contrast Volume (mL)	Parameter	Time Point	Stop Metformin Mean (SD)	Continue Metformin Mean (SD)	P-value (Between Groups)
80	Creatinine (mg/dL)	Before angiography	0.97 (0.06)	0.96 (0.07)	0.382†
		After angiography	1.01 (0.05)	1.03 (0.06)	0.212†
		One month after	0.98 (0.06)	0.99 (0.06)	0.489†
	GFR (mL/min/1.73 m²)	Before angiography	79.20 (8.10)	78.50 (8.00)	0.420†
		After angiography	76.20 (7.90)	74.00 (7.70)	0.150†
	Lactate (mmol/L)	Before angiography	1.45 (0.11)	1.46 (0.11)	0.570†
		After angiography	1.47 (0.12)	1.49 (0.12)	0.430†
	pH	Before angiography	7.38 (0.02)	7.38 (0.02)	0.645†
		After angiography	7.38 (0.02)	7.38 (0.02)	0.950†
100	Creatinine (mg/dL)	Before angiography	0.98 (0.06)	0.97 (0.06)	0.431†
		After angiography	1.02 (0.05)	1.04 (0.06)	0.205†
		One month after	0.99 (0.06)	1.00 (0.05)	0.457†
Effect of contrast volume (80 vs 100 mL) on renal, metabolic, and acid–base parameters in patients who discontinued compared with those who continued metformin therapy undergoing coronary angiography.					
• Data are presented as Mean (SD)					
• † Mann–Whitney U test (between-group comparisons)					
• Within-group comparisons were performed using Friedman or Wilcoxon signed-rank tests and showed no statistically significant differences					
• P < 0.05 was considered statistically significant					

Contrast Volume (mL)	Parameter	Time Point	Stop Metformin Mean (SD)	Continue Metformin Mean (SD)	P-value (Between Groups)
	GFR (mL/min/1.73 m ²)	Before angiography	82.00 (8.20)	81.60 (7.80)	0.605†
		After angiography	78.80 (7.90)	77.00 (7.60)	0.130†
	Lactate (mmol/L)	Before angiography	1.44 (0.12)	1.45 (0.11)	0.505†
		After angiography	1.46 (0.12)	1.48 (0.12)	0.360†
	pH	Before angiography	7.37 (0.01)	7.37 (0.02)	0.780†
		After angiography	7.37 (0.01)	7.37 (0.02)	0.870†
Effect of contrast volume (80 vs 100 mL) on renal, metabolic, and acid–base parameters in patients who discontinued compared with those who continued metformin therapy undergoing coronary angiography.					
• Data are presented as Mean (SD)					
• † Mann–Whitney U test (between-group comparisons)					
• Within-group comparisons were performed using Friedman or Wilcoxon signed-rank tests and showed no statistically significant differences					
• P < 0.05 was considered statistically significant					

Multivariable Analyses

To adjust for potential confounders, multivariable ANCOVA models were performed, incorporating baseline values, metformin dose, contrast volume, age, BMI, and gender as covariates.

Serum Creatinine

After adjustment (Table 4), discontinuation versus continuation of metformin was not independently associated with post-angiography serum creatinine ($B = -0.001$, $P = 0.639$). Baseline creatinine was the strongest predictor of post-procedure values ($B = 0.404$, $P < 0.001$). Higher metformin doses (1500 mg and 2000 mg) were independently associated with modestly higher creatinine ($P = 0.009$ and 0.001 , respectively), whereas contrast volume, age, BMI, and gender were not significant predictors.

Table 4

Association Between Metformin Discontinuation Versus Continuation and Post-Angiography Serum Creatinine After Adjustment for Baseline Creatinine, Metformin Dose, Contrast Volume, and Demographic Factors

Parameter	B	SE	t	P-value	95% Confidence Interval		Partial Eta Squared	Observed Power
					Lower	Upper		
Intercept	0.144	0.026	5.538	< 0.001	0.093	0.195		0.149
Group (Stop vs Continue)	-0.001	0.003	-0.470	0.639	-0.007	0.005		0.001
Gender (Male vs Female)	0.000	0.002	0.163	0.871	-0.004	0.005		0.000
Metformin Dose (1000 vs 500 mg)	0.003	0.004	0.711	0.478	-0.005	0.011		0.013
Metformin Dose (1500 vs 500 mg)	0.008	0.003	2.654	0.009	0.002	0.014		0.178
Metformin Dose (2000 vs 500 mg)	0.011	0.003	3.452	0.001	0.005	0.017		0.196
Contrast Volume (80 vs 100 mL)	0.003	0.003	1.009	0.314	-0.003	0.008		0.017
Baseline Creatinine	0.404	0.009	44.654	< 0.001	0.387	0.421		0.953
Age (years)	0.009	0.006	1.395	0.165	-0.004	0.023		0.030
BMI (kg/m ²)	0.000	0.001	0.240	0.811	-0.001	0.001		0.000

Parameter	B	SE	t	P-value	95% Confidence Interval	Partial Eta Squared	Observed Power
					Lower	Upper	
<i>Multivariable analysis of the association between metformin discontinuation versus continuation and post-angiography serum creatinine, adjusting for baseline creatinine, metformin dose, contrast volume, age, BMI, and gender.</i>							
Statistical Notes							
• Multivariable analysis of covariance (ANCOVA) model							
• Dependent variable: post-angiography serum creatinine							
• Reference categories:							
o Metformin dose: 500 mg/day							
o Contrast volume: 100 mL							
• $P < 0.05$ is considered statistically significant							
• Observed power calculated for each predictor							

GFR

Similarly, continuation of metformin was not independently associated with post-angiography GFR ($B = -0.031$, $P = 0.846$; Table 5). Baseline GFR remained the dominant predictor ($B = 0.929$, $P < 0.001$). Higher metformin doses (1500–2000 mg) were associated with significantly lower post-angiography GFR ($P < 0.001$), whereas contrast volume, age, BMI, and gender showed no significant effects.

Table 5

Multivariable Analysis of the Association Between Metformin Discontinuation Versus Continuation and Post-Angiography GFR, Adjusted for Baseline GFR, Metformin Dose, Contrast Volume, and Demographic Factors

Parameter	B	SE	t	P-value	95% Confidence Interval		Partial Eta Squared	Observed Power
					Lower	Upper		
Intercept	1.070	3.220	0.332	0.740	-5.283	7.423		0.001
Group (Stop vs Continue)	-0.031	0.160	-0.194	0.846	-0.347	0.285		0.000
Gender (Male vs Female)	-0.023	0.154	-0.152	0.879	-0.327	0.280		0.000
Metformin Dose (1000 vs 500 mg)	0.034	0.154	0.221	0.825	-0.270	0.338		0.001
Metformin Dose (1500 vs 500 mg)	-0.938	0.270	-3.474	< 0.001	-1.471	-0.405		0.148
Metformin Dose (2000 vs 500 mg)	-0.962	0.273	-3.524	< 0.001	-1.502	-0.422		0.152
Contrast Volume (80 vs 100 mL)	-0.017	0.278	-0.061	0.951	-0.563	0.530		0.000
Baseline GFR	0.929	0.021	44.012	< 0.001	0.888	0.970		0.910
Age (years)	-0.010	0.025	-0.376	0.707	-0.059	0.040		0

Parameter	B	SE	t	P-value	95% Confidence Interval	Partial Eta Squared	Observed Power
					Lower	Upper	
<i>Multivariable analysis of the association between metformin discontinuation versus continuation and post-angiography GFR, adjusting for baseline GFR, metformin dose, contrast volume, age, BMI, and gender.</i>							
Statistical Notes							
Dependent variable: Post-angiography GFR							
Analysis: Multivariable ANCOVA, adjusting for baseline GFR, metformin dose, contrast volume, age, BMI, and gender							
Reference categories:							
o Metformin dose: 500 mg/day							
o Contrast volume: 100 mL							
$P < 0.05$ is considered statistically significant							
Partial Eta Squared: effect size for each predictor							
Observed power calculated for each predictor							

Lactate

Metformin continuation was not independently associated with post-angiography lactate ($B = -0.005$, $P = 0.300$; Table 6). Baseline lactate strongly predicted post-procedure values ($B = 1.023$, $P < 0.001$). Higher doses of metformin (1500–2000 mg) were associated with modestly increased lactate ($P = 0.035$ and 0.023 , respectively), whereas other covariates were non-significant.

Table 6

Multivariable Analysis of the Association Between Metformin Discontinuation Versus Continuation and Post-Angiography Lactate, Adjusted for Baseline Lactate, Metformin Dose, Contrast Volume, and Demographic Factors

Parameter	B	SE	t	P-value	95% Confidence Interval		Partial Eta Squared	Observed Power
					Lower	Upper		
Intercept	0.033	0.048	0.688	0.494	-0.062	0.128	0.048	
Group (Stop vs Continue)	-0.005	0.005	-1.040	0.300	-0.014	0.004	0.023	
Gender (Male vs Female)	-0.002	0.005	-0.439	0.661	-0.011	0.007	0.005	
Metformin Dose (1000 vs 500 mg)	0.004	0.009	-0.445	0.657	-0.021	0.013	0.005	
Metformin Dose (1500 vs 500 mg)	0.012	0.006	-2.143	0.035	-0.024	-0.001	0.060	
Metformin Dose (2000 vs 500 mg)	0.013	0.007	-2.310	0.023	-0.024	-0.002	0.066	
Contrast Volume (80 vs 100 mL)	-0.003	0.005	-0.490	0.621	-0.013	0.008	0.006	
Baseline Lactate	1.023	0.020	51.033	< 0.001	0.984	1.063	0.971	
Age (years)	0.000	0.001	-0.280	0.758	-0.002	0.001	0.003	
BMI (kg/m ²)	0.000	0.001	-0.370	0.712	-0.002	0.002	0.004	

Parameter	B	SE	t	P-value	95% Confidence Interval	Partial Eta Squared	Observed Power
					Lower	Upper	
<i>Multivariable analysis of the association between metformin discontinuation versus continuation and post-angiography lactate levels, adjusting for baseline lactate, metformin dose, contrast volume, age, BMI, and gender.</i>							
Statistical Notes							
• Dependent variable: Post-angiography lactate							
• Analysis: Multivariable ANCOVA, adjusting for baseline lactate, metformin dose, contrast volume, age, BMI, and gender							
• Reference categories:							
o Metformin dose: 500 mg/day							
o Contrast volume: 100 mL							
• $P < 0.05$ is considered statistically significant							
• Partial Eta Squared: effect size for each predictor							
• Observed power calculated for each predictor							

pH

No independent association was observed between metformin continuation and post-angiography pH ($B = 0.000$, $P = 0.398$; Table 7). Baseline pH was the primary determinant of post-procedure pH ($B = 0.975$, $P < 0.001$). Metformin dose, contrast volume, age, BMI, and gender were not significant predictors.

Table 7

Multivariable Analysis of the Association Between Metformin Discontinuation Versus Continuation and Post-Angiography pH, Adjusted for Baseline pH, Metformin Dose, Contrast Volume, and Demographic Factors

Parameter	B	SE	t	P-value	95% Confidence Interval		Partial Eta Squared	Observed Power
					Lower	Upper		
Intercept	0.174	0.110	1.586	0.114	-0.042	0.390		0.028
Group (Stop vs Continue)	0.000	0.001	0.850	0.398	-0.001	0.001		0.011
Gender (Male vs Female)	0.000	0.000	0.873	0.384	-0.001	0.001		0.011
Metformin Dose (1000 vs 500 mg)	0.000	0.001	0.204	0.838	-0.002	0.003		0.005
Metformin Dose (1500 vs 500 mg)	-0.001	0.001	-1.500	0.136	-0.003	0.001		0.017
Metformin Dose (2000 vs 500 mg)	-0.001	0.001	-1.470	0.142	-0.003	0.001		0.016
Contrast Volume (80 vs 100 mL)	-0.001	0.001	-0.733	0.464	-0.002	0.001		0.006
Baseline pH	0.975	0.015	65.560	< 0.001	0.946	1.004		0.980
Age (years)	-7.29	4.15	-0.176	0.860	-8.90	7.44		0.001
BMI (kg/m ²)	0.000	0.000	1.035	0.302	-0.001	0.001		0.009

Parameter	B	SE	t	P-value	95% Confidence Interval	Partial Eta Squared	Observed Power
					Lower	Upper	
<i>Multivariable analysis of the association between metformin discontinuation versus continuation and post-angiography pH, adjusting for baseline pH, metformin dose, contrast volume, age, BMI, and gender.</i>							
Statistical Notes							
• Dependent variable: Post-angiography pH							
• Analysis: Multivariable ANCOVA, adjusting for baseline pH, metformin dose, contrast volume, age, BMI, and gender							
• Reference categories:							
o Metformin dose: 500 mg/day							
o Contrast volume: 100 mL							
• $P < 0.05$ considered statistically significant							
• Partial Eta Squared: effect size for each predictor							
• Observed power calculated for each predictor							

Discussion

Managing metformin in diabetic patients undergoing coronary angiography has traditionally been challenging due to concerns about contrast-induced acute kidney injury (CI-AKI) and the potential, though rare, risk of metformin-associated lactic acidosis (MALA) (13). Historically, guidelines recommended routine temporary discontinuation of metformin before contrast exposure. However, growing evidence indicates that in patients with normal or mildly impaired renal function, the risk of MALA is extremely low. The introduction of low-osmolality and iso-osmolar contrast media has further questioned the necessity of routine metformin interruption (14). Therefore, high-quality clinical data are needed to guide peri-procedural metformin management. This study was designed to evaluate the safety of continuing versus temporarily discontinuing metformin in a randomized controlled setting.

Effect of Metformin Continuation versus Discontinuation on Renal Function

Our analysis showed no statistically significant difference in post-angiography serum creatinine between patients who continued metformin and those who temporarily discontinued it. This indicates that continuing metformin in patients with preserved renal function does not increase the risk of CI-AKI.

The theoretical concern underlying metformin discontinuation relates to MALA. Impaired renal clearance due to contrast-induced nephropathy could theoretically lead to metformin accumulation and lactic acidosis (13). Nevertheless, MALA is exceedingly rare, generally occurring only in patients with severe renal impairment ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$) or profound hypoxic conditions (15). Epidemiologic studies estimate its incidence at roughly 3–10 cases per 100,000 patient-years, predominantly in high-risk populations (15). Our results support the consensus that for elective coronary angiography in patients with stable or mildly reduced renal function, metformin continuation is safe and does not meaningfully affect post-procedure renal outcomes.

The widespread use of low- or iso-osmolar contrast agents has reduced CI-AKI incidence, further supporting the safety of continued metformin therapy (16). Additionally, our cohort underwent elective procedures with standard pre- and post-procedure hydration protocols, a key preventive strategy against contrast-induced nephropathy (17).

Our results align with a growing body of literature and contemporary guideline recommendations. Both the American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR) now advise against routine metformin discontinuation in patients with stable $\text{eGFR} > 30 \text{ mL/min/1.73 m}^2$ (54,57). Our study confirms and extends these findings in a separate population, emphasizing that unnecessary metformin interruption may be avoided without compromising patient safety, thereby preventing potential hyperglycemia or treatment disruption.

Baseline Creatinine as a Predictor of Post-Procedural Renal Function

Consistent with established pathophysiology, baseline serum creatinine emerged as the strongest predictor of post-angiography creatinine. Pre-existing chronic kidney disease or even mild reductions in renal reserve are well-recognized risk factors for CI-AKI (18). Kidneys with prior injury are more susceptible to the nephrotoxic and hemodynamic effects of contrast (19). These findings highlight the importance of identifying high-risk patients based on baseline renal function and implementing preventive measures such as adequate hydration, rather than focusing solely on metformin management.

Dose-Dependent Effects of Metformin on Renal Function

Interestingly, higher metformin doses (1500 and 2000 mg/day) were associated with modest but statistically significant increases in post-angiography serum creatinine compared with the reference 500 mg/day dose. Metformin itself is not nephrotoxic (20); therefore, this association likely reflects residual confounding. Patients on higher metformin doses often have more severe or longstanding diabetes, poorer glycemic control, and higher baseline risk for diabetic kidney disease (21). Although our models adjusted for potential confounders, unmeasured variables may persist. Clinically, this suggests that patients on higher metformin doses represent a higher-risk phenotype and warrant closer monitoring, not necessarily because of the drug itself.

Effect on GFR

Consistent with creatinine findings, no significant association was observed between the study group and post-angiography GFR. This further reinforces the safety of metformin continuation in patients with preserved baseline renal function. These results corroborate current guidelines and systematic reviews, including a 2022 meta-analysis by Kao et al., which found no significant difference in GFR decline or CI-AKI incidence between continuation and discontinuation groups in patients with normal or mildly impaired renal function (9).

Lactate and pH

Our study demonstrated no significant association between study group and post-angiography lactate levels ($p = 0.300$), indicating that continuing metformin did not increase the risk of hyperlactatemia or MALA. Notably, higher metformin doses (1500 and 2000 mg/day) were associated with small, statistically significant increases in lactate; however, the magnitude was clinically negligible (e.g., $B = 0.013$ mmol/L for 2000 mg), well below thresholds for hyperlactatemia or lactic acidosis (22, 23). These minor elevations are likely a physiological consequence of metformin-induced inhibition of hepatic gluconeogenesis and enhanced anaerobic glycolysis, rather than a pathologic process (24, 25). Importantly, no effect on pH was observed, underscoring that these lactate changes did not translate into systemic acid-base disturbances.

Clinical Implications

Our findings provide strong evidence that peri-procedural continuation of metformin in diabetic patients with preserved renal function is safe with respect to both renal and metabolic outcomes. Baseline renal function, rather than metformin management, remains the primary determinant of post-procedural risk. High-dose metformin may serve as a marker of higher-risk patients rather than a causative factor. These results support recent guideline shifts advocating a less conservative approach to metformin management in this patient population (26).

Limitations and Future Directions

This study has several limitations that should be acknowledged. First, it was conducted at a single center, which may limit the generalizability of the findings to broader populations or different healthcare settings. Second, the study population primarily included patients with preserved or mildly impaired renal function undergoing elective coronary angiography; therefore, results may not be directly applicable to patients with advanced chronic kidney disease, emergent procedures, or other high-risk clinical scenarios. Third, certain potential confounding variables, such as glycemic control (e.g., HbA1c), duration of diabetes, and comorbidities not captured in the analysis, were not systematically assessed, which could influence renal and metabolic outcomes. Additionally, while the study was randomized, it was open-label, and the lack of full blinding may introduce bias in clinical management, although laboratory personnel were blinded to group allocation.

Future research should focus on multicenter trials with larger and more diverse patient populations, including those with lower baseline renal function or undergoing urgent interventions, to confirm the safety of continuing metformin across different risk strata. Incorporating longitudinal follow-up and comprehensive metabolic assessments, such as continuous glucose monitoring and detailed evaluation of lactate kinetics, may provide further insight into the long-term renal and metabolic consequences of peri-procedural metformin management. Moreover, stratified analyses based on metformin dose, concomitant medications, and severity of comorbidities could help refine individualized recommendations for peri-angiography metformin use.

Conclusion

In contemporary elective coronary angiography, continuation of metformin in patients with preserved renal function does not result in clinically relevant renal or metabolic injury. These findings support a selective, rather than routine, approach to peri-procedural metformin discontinuation.

Abbreviations

- ACE: Angiotensin-Converting Enzyme
- ANCOVA: Analysis of Covariance
- ARB: Angiotensin Receptor Blocker
- BMI: Body Mass Index
- CI-AKI: Contrast-Induced Acute Kidney Injury
- CKD: Chronic Kidney Disease
- Cr: Creatinine
- eGFR: Estimated Glomerular Filtration Rate
- EF: Ejection Fraction
- ESUR: European Society of Urogenital Radiology
- FBS: Fasting Blood Sugar
- GFR: Glomerular Filtration Rate
- MALA: Metformin-Associated Lactic Acidosis
- SD: Standard Deviation
- MRA: Mineralocorticoid Receptor Antagonist
- SPSS: Statistical Package for the Social Sciences
- T2DM: Type 2 Diabetes Mellitus
- V: Volume

Declarations

Funding

This research received no specific grant or funding from any public, commercial, or not-for-profit organizations.

Author Contribution

F.B., R.N., and S.P. conceptualized and designed the study. S.P. and A.S. oversaw data collection and ensured data quality. Y.H. and B.G. performed data analysis and prepared tables and figures. F.B. and R.N. drafted the manuscript. S.J. supervised the study, provided critical revisions, and finalized the manuscript. All authors reviewed and approved the final version.

Data Availability

Data are available upon reasonable request.

References

1. Vieira IH, Barros LM, Baptista CF, Rodrigues DM, Paiva IM. Recommendations for Practical Use of Metformin, a Central Pharmacological Therapy in Type 2 Diabetes. *Clin Diabetes*. 2022;40(1):97–107.
2. Hsu WH, Hsiao PJ, Lin PC, Chen SC, Lee MY, Shin SJ. Effect of metformin on kidney function in patients with type 2 diabetes mellitus and moderate chronic kidney disease. *Oncotarget*. 2018;9(4):5416–23.
3. Eppenga W, Lalmohamed A, Geerts A, Derijks HJ, Wensing M, Egberts T, et al. Risk of Lactic Acidosis or Elevated Lactate Concentrations in Metformin Users With Renal Impairment: A Population-Based Cohort Study. *Diabetes Care*. 2014;37:2218–24.
4. Kočka V. The coronary angiography – An old-timer in great shape. *Cor et Vasa*. 2015;57(6):e419–24.
5. Sůva M, Kala P, Poloczek M, Kaňovský J, Štípal R, Radvan M, et al. Contrast-induced acute kidney injury and its contemporary prevention. *Front Cardiovasc Med*. 2022;9:1073072.
6. Vasudev I, Bhardwaj A. Metformin in Focus: Systematic Review of Lactic Acidosis Risk and Outcomes, 2015–2025: TH-PO0385. *J Am Soc Nephrol*. 2025;36(10S).
7. Chiarito M, Sanz-Sanchez J, Piccolo R, Condello F, Liccardo G, Maurina M, et al. Safety of metformin continuation in diabetic patients undergoing invasive coronary angiography: the NO-STOP single arm trial. *Cardiovasc Diabetol*. 2023;22(1):28.
8. Hall N, Hall JE, Dobrzynski A. Evaluating Management and Change in Glycemic Control After Discontinuation of Metformin in Patients With Elevated Serum Creatinine. *Fed Pract*. 2017;34(Suppl 8):S44–8.
9. Kao TW, Lee KH, Chan WP, Fan KC, Liu CW, Huang YC. Continuous use of metformin in patients receiving contrast medium: what is the evidence? A systematic review and meta-analysis. *Eur*

- Radiol. 2022;32(5):3045–55.
10. Oktay V, Calpar Çıralı İ, Sinan ÜY, Yıldız A, Ersanlı MK. Impact of continuation of metformin prior to elective coronary angiography on acute contrast nephropathy in patients with normal or mildly impaired renal functions. *Anatol J Cardiol.* 2017;18(5):334–9.
 11. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol.* 2010;5(6):1003–9.
 12. Goodyear MD, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki. *BMJ.* 2007;335(7621):624–5.
 13. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA.* 2014;312(24):2668–75.
 14. Geenen RWF, van der Molen AJ, Dekkers IA, Bellin MF, Bertolotto M, Correias JM, et al. Contrast media for hysterosalpingography: systematic search and review providing new guidelines by the Contrast Media Safety Committee of the European Society of Urogenital Radiology. *Eur Radiol.* 2024;34(10):6435–43.
 15. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. *Metabolism.* 2016;65(2):20–9.
 16. Stacul F, van der Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol.* 2011;21(12):2527–41.
 17. Liu Y, Tan N, Huo Y, Chen S, Liu J, Chen YD, et al. Hydration for prevention of kidney injury after primary coronary intervention for acute myocardial infarction: a randomised clinical trial. *Heart.* 2022;108(12):948–55.
 18. Gouveia R, Bravo P, Santos C, Ramos A. Contrast-induced acute kidney injury – A review focusing on prophylactic strategies. *Angiologia e Cirurgia Vascular.* 2015;11(2):68–78.
 19. Hossain MA, Costanzo E, Cosentino J, Patel C, Qaisar H, Singh V, et al. Contrast-induced nephropathy: Pathophysiology, risk factors, and prevention. *Saudi J Kidney Dis Transpl.* 2018;29(1):1–9.
 20. Kawanami D, Takashi Y, Tanabe M. Significance of Metformin Use in Diabetic Kidney Disease. *Int J Mol Sci.* 2020;21(12).
 21. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. *Clin J Am Soc Nephrol.* 2017;12(12):2032–45.
 22. Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. *Mayo Clin Proc.* 2013;88(10):1127-40.
 23. Eppenga WL, Lalmohamed A, Geerts AF, Derijks HJ, Wensing M, Egberts A, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care.* 2014;37(8):2218–24.

24. Dutta S, Shah RB, Singhal S, Dutta SB, Bansal S, Sinha S, et al. Metformin: A Review of Potential Mechanism and Therapeutic Utility Beyond Diabetes. *Drug Des Devel Ther.* 2023;17:1907–32.
25. Lalau JD, Arnouts P, Sharif A, De Broe ME. Metformin and other antidiabetic agents in renal failure patients. *Kidney Int.* 2015;87(2):308–22.
26. Davenport MS, Perazella MA, Yee J, Dillman JR, Fine D, McDonald RJ, et al. Use of Intravenous Iodinated Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. *Radiology.* 2020;294(3):660–8.

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